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Ligand-Assisted Rate Acceleration in Transacylation by a Yttrium–Salen Complex. Demonstration of a Conceptually New Strategy for Metal-Catalyzed Kinetic Resolution of Alcohols

Mei-Huey Lin and T. V. RajanBabu*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

rajanbabu.1@osu.edu

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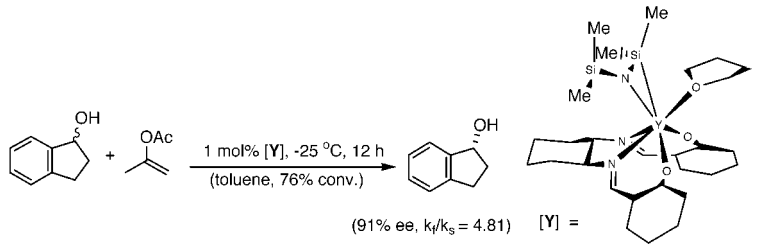
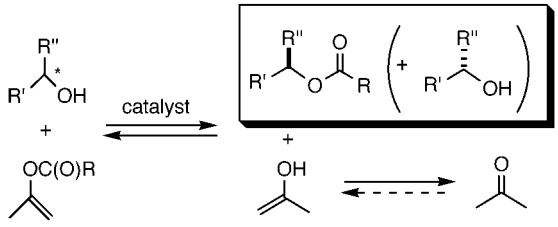
ABSTRACT



Yttrium-salen complexes effect transacylation between enolesters and chiral secondary alcohols, resulting in varying degrees of kinetic resolution. Even though the enantioselectivity remains modest (k_{fast}/k_{slow} up to 4.81), these results represent the first demonstration of a conceptually new metal-catalyzed acyl transfer process that results in kinetic resolution. On the basis of the solid-state structure of the catalyst, a novel associative mechanistic pathway is proposed for the reaction.

In this Letter we report the synthesis, characterization, and application of a class of yttrium complexes that catalyze enantioselective acyl transfer reactions between enolesters and secondary alcohols, resulting in kinetic resolution of the alcohols (Scheme 1)[1] In several instances, these Y-salen complexes have also been found to significantly enhance the rate of the acyl transfer process vis-á-vis the corresponding Y-alkoxides, enabling this reaction to be carried out at temperatures as low as −25 °C with 1 mol % of the catalyst. As a prelude to the present studies, last year we reported

Scheme 1. Kinetic Resolution via Enantiospecific Acyl Transfer



(1) For leading references for nonenzymatic kinetic resolution of alcohols, see: (a) Sekar, G.; Nishiyama, H. *J. Am. Chem. Soc.* **2001**, *123*, 3603. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (c) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. J. *Chem. Lett.* **1999**, *265*. (d) Yamada, S.; Katsumata, H. *J. Org. Chem.* **1999**, *64*, 9365. (e) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (f) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (g) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. Kinetic resolution of a diol: Iwasaki, F.; Maki, T.; Nakashima, W.; Onomura, O.; Matsumura, Y. *Org. Lett.* **1999**, *1*, 969. For a novel oxidative kinetic resolution, see: Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.

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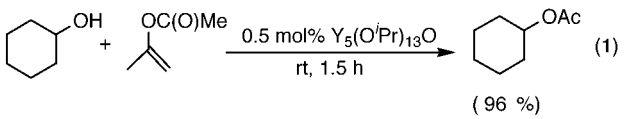
that primary and secondary alcohols react with enolesters at room temperature in the presence of catalytic amounts (0.05−1 mol %) of $Y_5(O^iPr)_{13}O$ or $Y(thd)_2(^iPrO)$ [thd = 2,2,6,6-tetramethyl-3,5-heptanedionato] to give the corresponding esters in nearly quantitative yields (eq 1).[2] On the



basis of the observation that a phenolic hydroxyl group is *not acylated* under these reaction conditions, we reasoned that salen-type ligands might be a rational first choice if we were to develop an enantiospecific version of this reaction. Accordingly, we prepared a variety of enantiopure salen and related ligands and their corresponding monomeric Y-complexes. Several of these complexes are efficient catalysts for acyl transfer reactions, some effecting the reaction with significant kinetic resolution when a racemic secondary alcohol is the substrate. Even though the degree of asymmetric induction remains modest, these results represent the first demonstration of a conceptually new metal-catalyzed process for the kinetic resolution of secondary alcohols. Our initial studies that validate the concept are reported here.

Prototypical examples of the ligands used in this study are shown in Figure 1.[3,4] The corresponding yttrium com-

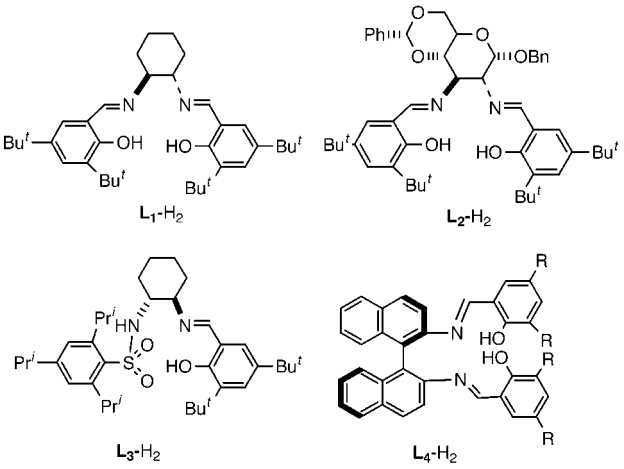


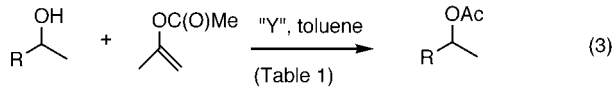
Figure 1. Selected ligands for yttrium in acyl transfer.

plexes were prepared by the extended silylamide route (eq 2).[5] A stoichiometric mixture of analytically pure ligand

$$Y[N(SiHMe_2)_2]_3{\cdot}2THF \xrightarrow[-\ 2HN(SiHMe_2)_2]{+\ \text{Ligand: (L-H}_2\text{)}} \mathbf{L}Y[N(SiHMe_2)_2][THF] \quad (2)$$

(**L**-H_2) and $Y[N(SiMe_2H)_2]_3{\cdot}2THF$ was stirred at room temperature in 1:1 hexane and THF (0.1 M) for 5 days and was concentrated to obtain the complexes, which were directly used for transesterification reactions in a hydrocarbon medium.[6] Recrystallization from pentane of the resulting product **1** ($\mathbf{L_1}Y[N(SiMe_2H)_2][THF]$) from the ligand $\mathbf{L_1}$-H_2 gave crystals suitable for X-ray analysis.[7]

The salen complexes of yttrium are excellent catalysts for the synthesis of esters via acyl transfer reactions from isopropenyl acetate as shown in eq 3 and Table 1. Several



1-phenylethanol
1-indanol, α-tetralol

alcohols are converted into the corresponding acetates in excellent yields with catalytic amounts (1−5 mol %) of the Y-salen complexes at or below room temperature (entries 5, 6, 9, and 11). For the three alcohols shown in Table 1, the Y-salen complexes are more efficient catalysts compared to the commercially available yttrium isopropoxide, $Y_5(O^iPr)_{13}O$. Thus 1-phenylethanol is converted into the

Table 1. Y-Catalyzed Acyl Transfer Reactions (eq 3)

no.	conditions	mol % Y	conv
	1-Phenylethanol		
1	11 mol % $HN(dms)_2$, rt, 16 h	0	0
2	5 mol % $\mathbf{L_1}$-H_2, rt, 22 h	0	0
3	1 mol % $Y_5(O^iPr)_{13}O$, −3 °C, 5.5 h	5	62
4	1 mol % $Y(\mathbf{L_1})(N(dms)_2(THF)$, −3 °C, 5.5 h	1	65
5	1 mol % $Y(O^iPr)_{13}O + 5\mathbf{L_1}$, −20 °C, 13 h	5	100
6	1 mol % $Y(\mathbf{L_1})(N(dms)_2(THF)$, 22 °C, 1 h	1	100
	1-Indanol		
7	1 mol % $Y_5(O^iPr)_{13}O$, −27 °C, 12 h	5	38
8	1 mol % $Y(\mathbf{L_1})(N(dms)_2(THF)$, −25 °C, 12 h	1	77
9	1 mol % $Y(\mathbf{L_1})(N(dms)_2(THF)$, −22 °C, 4 h	1	95
	α-Tetralol		
10	1 mol % $Y_5(O^iPr)_{13}O$, −22 °C, 24.5 h	5	35
11	1 mol % $Y_5(O^iPr)_{13}O + 5\ \mathbf{L_1}$, 22 °C, 0.5 h	1	97
12	1 mol % $Y(\mathbf{L_1})(N(dms)_2(THF)$, 22 °C, 4 h	1	51

(2) Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 997. For an example of a lanthanide-catalyzed transesterification, see: Okano, T.; Miyamoto, K.; Kiji, J. *Chem. Lett.* **1995**, 246.

(3) See Supporting Information for a more complete list of ligands, their preparation and characterization, and experimental details of their utility in various acyl transfer reactions.

(4) For a review of metal-salen complexes in asymmetric synthesis, see: Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85. For some recent notable applications of these ligands, see ($\mathbf{L_1}$): (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; p 649. Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601. ($\mathbf{L_3}$): (c) Balsells, J.; Walsh, P. J. *J. Org. Chem.* **2000**, *65*, 5005. ($\mathbf{L_4}$): (d) Spassky, N.; Wisniewski, M.; Pluta, C.; Le Borgne, A. *Macromol. Chem. Phys.* **1996**, *197*, 2627. (f) Evans, D. A. Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884.

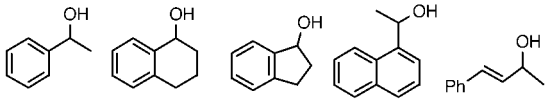
(5) (a) Herrmann, W. A.; Anwander, R.; Munck, F. C.; Scherer, W.; Dufaud, V.; Huber, N. W.; Artus, G. R. J. *Z. Naturforsch., B*: *Chem. Sci.* **1994**, *49*, 1789. (b) Runte, O.; Priermeier, T.; Anwander, R. *J. Chem. Soc., Chem. Commun.* **1996**, 1385. (c) Evans, W. J.; Fujimoto, C. H.; Ziller, J. W. *J. Chem. Soc., Chem. Commun.* **1999**, 311.

corresponding acetate upon reaction with isopropenyl acetate in the presence of 1 mol % of the aggregate $Y_5(O^iPr)_{13}O$ (5 mol % in Y) in 62% yield at −3 °C in 5.5 h (entry 3), whereas the salen complex **1** (Y[$\mathbf{L_1}$][THF][$N(SiHMe_2)_2$]) effects the same conversion with 1 mol % Y (entry 4) during the same reaction time. A catalyst prepared by addition of stoichiometric amount of the ligand $\mathbf{L_1}$ to $Y_5(O^iPr)_{13}O$ followed by removal of the volatile side products also provides enough enhancement of the rate of acylation of the alcohols to allow a quantitative reaction to be carried out at −20 °C (entry 5). The Y-salen complex is also a relatively superior catalyst for the acylation of 1-indanol (entries 7 and 8). Entries 10−12 document a similar effect on the acylation of α-tetralol. Control experiments show that in the absence of Y, there is no reaction between an enolester and an alcohol (entries 1 and 2).[3]

In earlier investigations[2] we had recognized the unique ability of yttrium alkoxides to effect the transacylation reaction. Since the Lewis acidity of the metal is likely to be an important consideration in any mechanistic scenario (vide infra), we also examined complexes of a number of other metals including the well-known salen complexes $\mathbf{L_1}$Mn(Cl), $\mathbf{L_1}$Cr(Cl), and $\mathbf{L_4}$Al(OMe). None showed any activity in the acyl transfer reactions. A scandium complex, $\mathbf{L_1}$Sc($N(SiMe_2H)_2$) (prepared from $Sc[N(SiMe_2H)_2]_3$·THF and $\mathbf{L_1}$) was found to be less active compared to the corresponding Y complex. In sharp contrast to $Y[(NSiMe_2H)_2]_3$·*n*THF, the corresponding scandium complex, $Sc[N(SiMe_2H)_2]_3$·THF, is not catalytically competent. A chloride-bridged Y-dimer, [($\mathbf{L_1}$)Y(μ-Cl)THF]$_2$,[3,8] also showed no catalytic activity, even in the presence of added silver salts such as AgOTf or AgOTf and Ph_3P. A carefully chosen set of Lewis acids,[9] among them bis(oxazoline) (BOX) and bisoxazolinylpyridine (PYBOX) complexes of Cu and Sn with various counteranions, were also examined as potential catalysts for the transacylation reaction. None offered any advantages over the yttrium complexes. In most instances, the reactions were complicated by the formation of unwanted side products. A study of the solvent effect revealed that aromatic hydrocarbons such as toluene and benzene were optimum. Dichloromethane was marginally useful, while solvents containing heteroatoms, (e.g, THF or CH_3CN) retarded the reaction, even when they were used as cosolvents.

In initial scouting experiments various alcohols **2**−**6** were subjected to kinetic resolution using the [$\mathbf{L_1}$]Y[$N(SiMe_2H)_2$]-[THF] as catalyst, and the results are shown in Table 2.[6] As

Table 2. Y($\mathbf{L_1}$)N(dms)$_2$(THF)-Catalyzed Kinetic Resolution[a]

R-OH: 

2 **3** **4** **5** **6**

entry	alcohol	Y (mol %)	°C	h	conv	% ee[b]	k_f/k_s
1	**2**	1	−3	5.6	65	23 (*S*)	1.50
2	**3**	2	−10	8	39	14 (*R*)	1.78
3	**4**	1	−25	12	76	91 (*R*)	4.81
4	**5**	1	−3	7.5	61	36 (*S*)	2.18
5	**6**	2	−10	9	42	13 (*S*)	1.60

[a] For procedure, see text. [b] Percent ee (HPLC) of unconverted alcohol.

with other methods of kinetic resolutions based on the acylation reaction,[1] the kinetic selectivity as measured by the *s* factor (k_{fast}/k_{slow})[10] varies considerably with the structure of the alcohol, with 1-indanol providing the highest ee for the unreacted alcohol (entry 3). A number of enol esters derived from other ketones and aldehydes were tested in the reaction. Even though we noticed considerable difference in the reactivities of these enolesters, none gave selectivity higher than isopropenyl acetate.[11]

Next the effect of the structure of the salen ligand on the kinetic resolution of 1-indanol (**4**) and 1-(1-naphthyl)ethanol (**5**) using 2-propenyl acetate as the acyl transfer agent was examined; the results are shown in Table 3**.** As can be seen

Table 3. Ligand Effects in Y-Catalyzed Kinetic Resolution

entry	alcohol	**L** (mol % Y)	conditions/conv (%)	% ee	k_f/k_s
1	**4**	$\mathbf{L_1}$ (1)	−25 °C, 12 h/77	91	4.81
2	**4**	$\mathbf{L_2}$ (1)	−25 °C, 12 h/40	26	2.83
3	**4**	$\mathbf{L_3}$ (1)	−12 °C, 18 h/80	85	3.50
4	**5**	$\mathbf{L_1}$ (1)	−3 °C, 7.5 h/61	36	2.18
5	**5**	$\mathbf{L_2}$ (1.5)	−3 °C, 9 h/69	61	2.97
6	**5**	$\mathbf{L_3}$ (1.5)	−3 °C, 11 h/29	15	2.54

from the Table, the two alcohols have widely different reactivities, 1-indanol being more reactive. Indanol also shows much better selectivity in the kinetic resolution under these reaction conditions with $\mathbf{L_1}$ and $\mathbf{L_3}$, whereas $\mathbf{L_2}$ gives better selectivity in the acylation of **5**. The sulfonamide complex (entries 3 and 6) is less active.

While the mechanism of this remarkable reaction remains to be elucidated, the solid-state structure of the catalyst,

(6) **Typical Experimental Procedure for Transacylation.** A mixture of alcohol (1 mmol) and the Y-catalyst in toluene (1.5 mL) was cooled to the indicated temperature under nitrogen, and the enol acetate (1.27 mmol) was added. At the end of the prescribed time, the cold solution was poured into water, and the products were extracted with ether. The ether solution was washed with saturated NaCl and dried, and the products were isolated by column chromatography. The ee's of unreacted alcohols were determined by chiral HPLC. See Supporting Information for details.

(7) Crystallographic data (excluding structure factors) for the structure of **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-181773. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB12EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk. See Supporting Information for details.

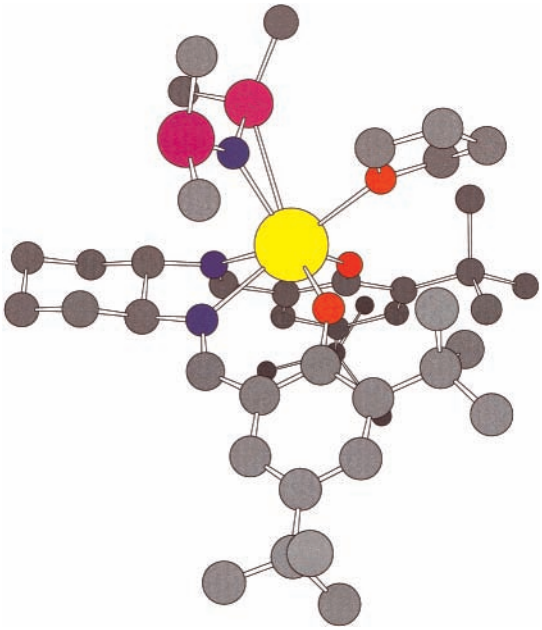
(8) For a related complex, see ref 5c.

(9) For a leading reference, see: Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; p 1177.

(10) Kagan, H. B.; Fiaud, J. C. *Topics Stereochem.* **1988**, *18*, 249.

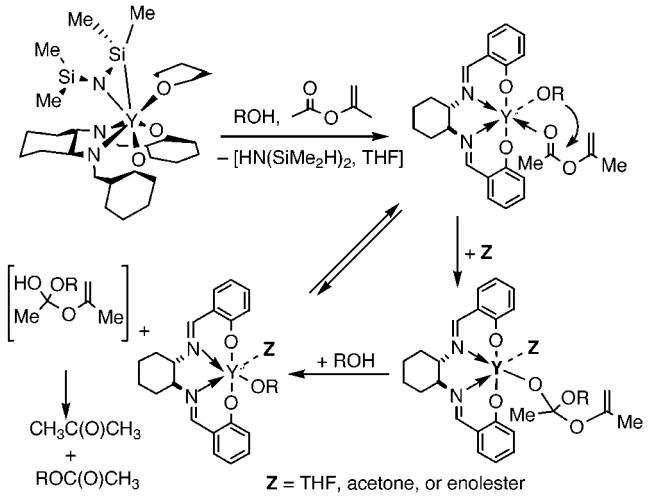
(11) The following ketones (with their *s* values shown in the bracket) were tested the for acylation of 1-indanol: *tert*-butyl methyl ketone (1.33, 22 °C), 4-methylacetophenone (1.30, 22 °C), isobutyraladehyde (2.60, −3 °C), cyclohexanone (1.67, −15 °C), (−)-menthone (1.5, −15 °C), and camphor (1.00, −15 °C). Most remarkably, the enolacetate derived from (+)-menthone showed no reactivity at −15 °C (0% conversion!) under conditions where the corresponding (-)-menthone enolacetate gave 59% conversion. We saw the same behavior in the acylation of α-tetralol but not in the acyclic alcohols. See Supporting Information for details.

which incorporates one anionic ligand [$^{-}$N(SiHMe$_2$)$_2$] and one neutral ligand (THF), suggests an attractive possibility.[12] Note that it has a distorted trigonal prismatic structure rather than the familiar octahedral geometry seen in most transition metal salen complexes. The large yttrium atom is placed 0.95 Å above the N_2O_2 plane. Replacement of the two ligands by an alkoxide (anionic) and an enol ester (neutral) could lead to activation of both these reactants within the coordination sphere of yttrium.



If the intermediate retains the distorted trigonal prismatic structure of the starting complex, the two reacting partners will be held closer in a "*cis*" orientation. An internal nucleophilic attack by the alkoxide on the carbonyl group could initiate a chain of events leading to the final products (Scheme 2). In accordance with such a mechanism, preliminary kinetic studies suggest that the reaction is first order in the catalyst. Further studies to elucidate the mechanism of the reaction and expand its scope through the use of other ligands are in progress.

Scheme 2. Possible Mechanism for the Acyl Transfer Process



In summary, the first example of a transition-metal-catalyzed asymmetric acyl transfer reaction is reported. Mild reaction conditions, high turnover frequency of the catalyst, and prospects of ligand tuning to improve the kinetic selectivity provide ample incentives for further research in the area.

Acknowledgment. We acknowledge the financial assistance by the Petroleum Research Fund (ACS) and U.S. National Science Foundation (CHE 0079948). We thank Dr. Judith C. Gallucci for the X-ray structure determination.

Supporting Information Available: Experimental details on the synthesis and utility of the complete set of ligands showing conversions and enantiomeric excesses and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The structure also reveals an unusual agostic interaction between one of the Si atoms and Y, presumably brought about by the chiral backbone. In a related salen complex prepared from 1,2-ethylenediamine, this interaction is absent.[5b] These structural aspects will be addressed separately.